REMARKS

Applicants thank Examiners Kosson and Weber for the helpful personal interview of March 26, 2008. This amendment is responsive to the discussion during that interview. The Interview Summary for the March 26th interview was submitted previously (May 7, 2008).

Applicants appreciate the further telephonic interview with Examiner Kosson on September 26th. Proposed claim amendments were discussed as summarized herein.

With this paper, claim 8 has been amended to include the limitation that "the botulinum neurotoxin is derived from one of botulinum toxin type A, B, C, D, E, or F" to emphasize that Applicants' neurotoxin utilizes heavy and light chains from the same serotype as discussed further below. Responsive to an issue raised during the telephonic interview of September 26th, claim 8 has been further amended to clarify that the purified botulinum neurotoxin is free from all non-toxic proteins in the complex.

Claims 8-11, 13, and 15-16 are now pending in this application. Support for the amendments is found in the existing claims and the specification as discussed below. Accordingly, the amendments do not constitute the addition of new matter. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

Rejection under 35 U.S.C. § 103(a)

Claims 8, 9, 12, 13, 15, and 16 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Borodic (US 5,183,462) in view of Johnson, et al. (US 5,939,070).

As discussed in the personal interview of March 26, 2008, Johnson, et al. is directed to "hybrid botulinal neurotoxin comprising heavy and light chain combinations that are not present in nature" (col. 4, lines 31-33). "The hybrid toxin molecule contains components that are not found together in their natural form" (see col. 5, lines 18-22). This means combining heavy and light chains from two different serotypes (col. 5, lines 23-31).

In contrast, Applicants' claimed invention is directed to "purified botulinum neurotoxin from a botulinum toxin complex, that is free from all non-toxic proteins in the complex," (claim 8, as amended). The phrase "purified botulinum neurotoxin" is explained in the present specification at page 5, paragraph 4 as:

> A purified botulinum neurotoxin as used herein means a neurotoxin that is separated from a non-toxic protein constituting a botulinum toxin. Such a neurotoxin can be obtained by a purifying process including (1) a step of decomposing a botulinum toxin (a progenitor toxin) into a neurotoxin and a non-toxic protein and (2) a step of separating the neurotoxin from the non-toxic protein.

In other words, the "purified botulinum neurotoxin" is a native neurotoxin. It is not the hybrid botulinal neurotoxin of Johnson, et al. While the present application mentions that the progenitor toxin may be cleaved with trypsin (present specification, page 6, last paragraph), there is no disclosure of recombining toxin heavy and light chains from different serotypes as in Johnson, et al. The present application utilizes the native neurotoxin without the need to mix serotypes contrary to the teaching of Johnson, et al.

Additionally, claim 8 has been amended to clearly distinguish the claimed invention from Johnson, et al and Borodic by inclusion of the limitation "wherein the botulinum neurotoxin is derived from one of botulinum toxin type A, B, C, D, E, or F." Support for the amendment is found in canceled claim 12 and generally in the description for purification of neurotoxin (page 5, paragraph 4 to page 7, 3rd full paragraph). The present specification contains no description of isolation of heavy and light chains and recombining from different serotypes as in Johnson, et al. Specific support for purification of types A and B neurotoxins is found in Examples 1 and 2 of the present specification. Claim 8 as amended clearly states that the neurotoxin is isolated from a single serotype, not multiple serotypes and recombined as in Johnson, et al. Accordingly, Johnson, et al. teach away from the claimed invention.

Johnson, et al suggest that by using the heavy chain from one serotype and the light chain from another serotype, that "it may be possible to use conjugates that contain the light chain of type A neurotoxin to treat dystonias in patients that are showing immunity to type A neurotoxin since a majority of the antibodies the patient produces are directed toward the heavy chain of the native type A neurotoxin" (col 11, lines 20-25).

However, the unexpected benefit of the present invention is that the problem of antigenicity is addressed by use of the purified neurotoxin without resorting to recombining heavy and light chains from different serotypes. As shown in the specification, the purified neurotoxin prepared according to the invention had low antigenicity compared with the progenitor toxin. As shown in Table 5 of Example 4 (page 22 of the present specification),

antibodies formed in the mouse immunized with the progenitor toxin but not with the mouse immunized with the purified neurotoxin according to the claimed invention. This result was unexpected in view of Johnson, et al. Based upon Johnson, et al., one of ordinary skill in the art would have expected that it would be necessary to combine heavy and light chains from different serotypes in order to reduce antigenicity.

Regarding Borodic, Borodic does not teach or suggest "a purified botulinum neurotoxin from a botulinum toxin complex, that is free from all non-toxic proteins in the complex". Borodic teaches the progenitor toxin.

Furthermore, while Applicants admit that Johnson, et al. do teach a purified botulinum neurotoxin, per se, Applicants continue to stress that Johnson, et al. are completely silent on the use of their hybrid neurotoxins. As Johnson, et al. do not teach the use of ANY butulinal neurotoxin for muscle hyperactivity, one of ordinary skill in the art faced with the teaching of Johnson, et al., would use non-toxic complexing proteins for stability in view of their known effects on stabilization of the labile neurotoxin. As indicated in Johnson, et al., such complexing proteins are "essential for stabilization" (col. 1, lines 62-64). Johnson, et al., at col. 2, lines 5-10 further teach that:

> Presumably, the complexing proteins protect the very labile toxin molecule from proteolytic cleavage and other types of inactivation by enzymes present in the gut and circulatory systems since the toxin and the complexing proteins are very stable in low pH environments

In view of the teaching of Johnson, et al., as well as the description of Borodic, which teaches the complex including non-toxic proteins, the use of a purified Botulinin neurotoxin free of non-toxic proteins from the complex to treat muscle hyperactivity as claimed was not obvious at the time of the claimed invention.

Furthermore, neither Borodic nor Johnson, et al. teach or suggest that antigenicity is reduced by administration of the purified neurotoxin without non-toxic proteins of the complex. Accordingly, the cited references, taken separately or together, do not teach or suggest all of the claim limitations.

Additionally, Johnson, et al. teach away from the claimed invention in their disclosure that the use of heavy and light chains from different serotypes is responsible for reducing antigenicity. In view of the teaching of Johnson, et al,. Applicants' result that the purified

neurotoxin has much lower antigenicity than the progenitor toxin was non-obvious and unexpected.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 8, 9, 12, 13, and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Donovan (US 2001/0053369) in view of Johnson, et al. (US 5,939,070).

Johnson, et al. has been discussed above. These comments are incorporated here by reference.

The disclosure of Donovan is similar to the disclosure of Borodic, above. That is, Donovan teaches the use of the botulinum toxin complex including the non-toxic proteins of the complex (i.e., BOTOX) in the treatment of a movement disorder. Donovan does not teach a purified botulinum neurotoxin. While, Johnson, et al. teach a purified botulinum neurotoxin, Johnson, et al. teach away from the claimed invention in directing one of ordinary skill in the art to use heavy and light chains of different serotypes so that the neurotoxin may have reduced antigenicity. Based upon Johnson, et al., one of ordinary skill in the art would not expect a purified neurotoxin with heavy and light chains from the same serotype to have the property of low antigenicity. This unexpected property is only known from Applicants' disclosure.

Additionally, claim 8 is clearly distinguished from Johnson, et al and Borodic by amendment to include the limitation that "the botulinum neurotoxin is derived from one of botulinum toxin type A, B, C, D, E, or F." Support for the amendment is found in canceled claim 12 and generally in the description for purification of neurotoxin (page 5, paragraph 4 to page 7, 3rd full paragraph). There is no description of isolation of heavy and light chains and recombining from different serotypes as in Johnson, et al. Specific support for types A and B neurotoxins is found in Examples 1 and 2 of the present specification. Claim 8 as amended clearly states that the neurotoxin is isolated from a single serotype, not multiple serotypes and recombined as in Johnson, et al.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 8-13, 15, and 16 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Aoki, et al. (US 6,319,505) in view of Johnson, et al. (US 5,939,070) and Allergan, Inc. (package insert for BOTOX, printed December 13, 2005).

As clarified during the interview of March 26, 2008, the BOTOX package insert is not prior art as it was published after Applicants' filing date.

Johnson, et al. have been discussed above. These comments are incorporated herein by reference.

Regarding Aoki, et al., this reference is similar to Borodic and Donovan discussed above. That is, while Aoki, et al. teach treatment of a muscle movement disorder (muscle spasm), Aoki, teach the use of the Botulinum neurotoxin complex including the non-toxic complexing proteins BOTOX, DYSPORT). Aoki, et al. do not teach treatment with the purified neurotoxin without the non-toxic complexing proteins.

While, Johnson, et al. teach a purified botulinum neurotoxin, Johnson, et al. teach away from the claimed invention in directing one of ordinary skill in the art to use heavy and light chains of different serotypes so that the neurotoxin may have reduced antigenicity. Based upon Johnson, et al., one of ordinary skill in the art would not expect a purified neurotoxin with heavy and light chains from the same serotype to have the property of low antigenicity. This unexpected property is only known from Applicants' disclosure.

Additionally, claim 8 is clearly distinguished from Johnson, et al and Borodic by amendment to include the limitation "wherein the botulinum neurotoxin is derived from one of botulinum toxin type A, B, C, D, E, or F." Support for the amendment is found in canceled claim 12 and generally in the description for purification of neurotoxin (page 5, paragraph 4 to page 7, 3rd full paragraph). There is no description of isolation of heavy and light chains and recombining from different serotypes as in Johnson, et al. Specific support for types A and B neurotoxins is found in Examples 1 and 2 of the present specification. Claim 8 as amended clearly states that the neurotoxin is isolated from a single serotype, not multiple serotypes and recombined as in Johnson, et al.

Regarding claims 10 and 11, neither Aoki, et al. nor Johnson, et al. teach stabilization of purified neurotoxin with "a botulinum neurotoxin-stabilizing substance other than the non-toxic protein of the botulinum toxin (claim 10) such as human serum albumin (claim 11). While Aoki,

et al. teach the use of albumin as stabilizer (col. 4, first full paragraph), there is nothing in either Johnson, et al nor Aoki, et al. that would suggest that albumin would be effective in stabilization of the purified neurotoxin in the absence of the non-toxic protein of the complex as the purified neurotoxin is known to be extremely labile. As indicated in Johnson, et al., such complexing proteins are "essential for stabilization" (col. 1, lines 62-64). Johnson, et al., at col. 2, lines 5-10 further teach that:

> Presumably, the complexing proteins protect the very labile toxin molecule from proteolytic cleavage and other types of inactivation by enzymes present in the gut and circulatory systems since the toxin and the complexing proteins are very stable in low pH environments

Accordingly, one of ordinary skill in the art would not expect that albumin or other neurotoxin-stabilizing substance could stabilize the purified botulinum neurotoxin in the absence of non-toxic stabilizing proteins of the complex.

In view of Applicants' arguments and amendments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 8, 9, 12, 13, 15, and 16 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Graham (US 6,395,277) in view of Johnson, et al. (US 5,939,070), Allergan, Inc. package insert (printed on December 13, 2005) and Shore Laser (printed on December 13, 2005).

As clarified during the interview of March 26, 2008, the BOTOX package insert and Shore Laser article are not prior art as they were both published after Applicants' filing date.

Like Borodic, Donovan, and Aoki, et al. discussed above, Graham, et al. merely teach the use of a botulinum neurotoxin complex, which includes the non-toxic complexing proteins (i.e. BOTOX) in a method of treating a muscle disorder, in this case relating to cerebral palsy. As in the rejections above, Johnson, et al. is cited for their teaching on a purified botulinum neurotoxin.

While, Johnson, et al. teach a purified botulinum neurotoxin, Johnson, et al. teach away from the claimed invention in directing one of ordinary skill in the art to use heavy and light chains of different serotypes so that the neurotoxin may have reduced antigenicity. Based upon Johnson, et al., one of ordinary skill in the art would not expect a purified neurotoxin with heavy

and light chains from the same serotype to have the property of low antigenicity. This unexpected property is only known from Applicants' disclosure.

Additionally, claim 8 is clearly distinguished from Johnson, et al and Borodic by amendment to include the limitation that "the botulinum neurotoxin is derived from one of botulinum toxin type A, B, C, D, E, or F." Support for the amendment is found in canceled claim 12 and generally in the description for purification of neurotoxin (page 5, paragraph 4 to page 7, 3rd full paragraph). There is no description of isolation of heavy and light chains and recombining from different serotypes as in Johnson, et al. Specific support for types A and B neurotoxins is found in Examples 1 and 2 of the present specification. Claim 8 as amended clearly states that the neurotoxin is isolated from a single serotype, not multiple serotypes and recombined as in Johnson, et al.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the

application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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